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10/590,661	08/25/2006	Hiroaki Hayashi	Q96763	2141
65565	7590	11/12/2008		
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WASHINGTON, DC 20037-3213				
EXAMINER				
STEADMAN, DAVID J				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/590,661

**Applicant(s)**

HAYASHI ET AL.

**Examiner**

David J. Steadman

**Art Unit**

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 31 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,5-8 and 10-16 is/are pending in the application.
- 4a) Of the above claim(s) 12-16 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 11 is/are allowed.
- 6) ☒ Claim(s) 1,3,5,6,8 and 10 is/are rejected.
- 7) ☒ Claim(s) 2 and 7 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 December 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☒ Other: Appendix A sequence alignment

**DETAILED ACTION**

***Status of the Application***

- [1] Claims 1-3, 5-8, and 10-16 are pending in the application.
- [2] Applicant's amendment to the claims, filed on 7/31/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. By the instant claim amendment, claims 1-3, 5-8, 10, and 12 are amended and claims 4 and 9 are canceled.
- [3] Applicant's amendment to the specification, filed on 7/31/08, is acknowledged.
- [4] Applicant's arguments filed on 7/31/08 in response to the Office action mailed on 4/11/08 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
- [5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

***Election/Restriction***

- [6] Claims 12-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/25/08.

***Claim for Priority***

[7] As noted in the prior Office action, this application is a 35 U.S.C. 371 national stage filing of PCT/JP05/03205, filed on 2/25/05, which claims foreign priority under 35 U.S.C. 119(a) to (d) to Japanese application 2004-049123, filed on 2/25/04. A certified copy of each of the Japanese priority document has been filed in the instant application on 8/25/06.

***Specification/Informalities***

[8] The specification is objected to as identifying “CYP93E1” as being SEQ ID NO:8 (see, e.g., specification at p. 23, paragraph 35, line 8). Based on a nucleic acid alignment between CYP93E1 and SEQ ID NO:8, the nucleotide sequences of CYP93E1 and SEQ ID NO:8 are distinct – where SEQ ID NO:8 has a G at position 121, CYP93E1 has an A at this corresponding position (see Office action mailed on 4/11/08, Appendix A sequence alignment). Since it appears that applicant intends for the nucleotide sequence of SEQ ID NO:8 to be identical to the prior art sequence of CYP93E1, is this an editing error, where position 121 of SEQ ID NO:8 should be A instead of G? Appropriate correction and/or clarification is required.

***Claim Objection***

[9] Claim 5 is objected to in the recitation of “claim 43” as there is no claim 43 present in the claim listing. In the interest of advancing prosecution, claim 5 has been interpreted as being dependent upon claim 3, not claim 43. Appropriate correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

**[10]** The written description rejection of claims 6, 8, and 10 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See paragraph 11 beginning at p. 6 of the 4/11/08 Office action.

RESPONSE TO ARGUMENT: Beginning at p. 10 of the instant remarks, applicant argues the genus of polynucleotides is adequately described in view of the claim amendment to limit the members of the genus to "encoding for a polypeptide of SEQ ID NO:9".

Applicant's argument is not found persuasive. MPEP 2111 directs the examiner to give claims their broadest reasonable interpretation. In view of the recitation of the grammatically indefinite article "a" in the phrase "a polypeptide of SEQ ID NO:9", this phrase has been interpreted as meaning any contiguous amino acid sequence of SEQ ID NO:9 of as few as two amino acids. In view of this broad but reasonable interpretation, the phrase "a polynucleotide encoding a polypeptide of SEQ ID NO:9" need only encode at least two contiguous amino acids of SEQ ID NO:9 and can encode any additional amino acid sequence at its 5'- and/or 3'-end(s). Thus, the members of the genus need only share a structural feature that encodes as few as two contiguous amino acids of SEQ ID NO:9.

While it is acknowledged that this structural feature must be shared by all members of the genus, it is not such a significant structural feature that would

distinguish the members of the genus from other polynucleotides such that a skilled artisan would recognize that applicant was in possession of all polynucleotides encompassed by the genus. Moreover, there is no disclosed or art recognized correlation between amino acids or regions of SEQ ID NO:9 that can be altered with an expectation of maintaining the activity of hydroxylating an oleanane-type triterpene at position 24.

It is noted that while similar language appears in claim 1, the encoded polypeptide of claim 1 is functionally limited to those that hydroxylate the 24-position of an oleanane type triterpene, while the encoded polypeptide of claim 6 is not.

Also, while the written description rejection set forth 4/11/08 Office action addressed the genus of beta-amyrin synthase genes, since beta-amyrin synthase genes appear to have been known in the art at the time of the invention and the novelty does not appear to reside in the genus of beta-amyrin synthase genes, the description of the genus of beta-amyrin synthase genes is no longer at issue.

**[11]** The scope of enablement rejection of claim(s) 6, 8, and 10 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See paragraph 12 beginning at p. 9 of the 4/11/08 Office action.

**RESPONSE TO ARGUMENT:** Beginning at p. 13 of the instant remarks, applicant argues the specification provides ample disclosure regarding how to make and use the full scope of recited polynucleotides, including, e.g., methods of isolating

nucleic acids and methods for assaying the encoded polypeptides for those that have the activity of hydroxylating a triterpene compound at position 24.

Applicant's argument is not found persuasive. It is the examiner's position that the specification is enabling only for an expression vector comprising a polynucleotide encoding the polypeptide of SEQ ID NO:9 and a  $\beta$ -amyrin synthase gene.

MPEP 2111 directs the examiner to give claims their broadest reasonable interpretation. In view of the recitation of the grammatically indefinite article "a" in the phrase "a polypeptide of SEQ ID NO:9", this phrase has been interpreted as meaning any contiguous amino acid sequence of SEQ ID NO:9 of as few as two amino acids. In view of this broad but reasonable interpretation, the phrase "a polynucleotide encoding a polypeptide of SEQ ID NO:9" need only encode at least two contiguous amino acids of SEQ ID NO:9 and can encode any additional amino acid sequence at its 5'- and/or 3'-end(s). Thus, the scope of recited polynucleotides encompasses those that encode as few as two contiguous amino acids of SEQ ID NO:9, including polynucleotides encoding polypeptides that have no functional relationship to SEQ ID NO:9, *e.g.*, non-functional, catalytically inactive polypeptides. The specification fails to provide any guidance for using an expression vector that encodes polypeptides having activity other than hydroxylating the 24-position of an oleanane-type triterpene. Also, the specification fails to provide guidance regarding those amino acids or regions of SEQ ID NO:9 that may be altered and still maintain the activity of hydroxylating the 24-position of an oleanane-type triterpene and it is highly unpredictable as to the effects of amino acid substitution on the activity of a polypeptide. While methods of isolating or generating variants of a

polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen – by a purely trial and error process – for all polynucleotide variants having a substantial number of modifications as encompassed by the claims for those that encode polypeptides having a desired activity/utility.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of required experimentation, it is the examiner's position that undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

**[12]** The enablement rejection of claim 11 under 35 U.S.C. 112, first paragraph, based upon a biological deposit, is withdrawn in view of applicant's submission of a statement filed on 8/30/08, asserting that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent.



***Claim Rejections - 35 USC § 102***

**[13]** Claim(s) 1 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Steele et al. (*Arch. Biochem. Biophys.* 367:146-150, 1999; cited in the IDS filed on 8/25/06; "Steele") as evidenced by Shibuya et al. (*FEBS J.* 273:948-959, 2006; cited in the 4/11/08 PTO-892; "Shibuya"). See MPEP 2131.01 regarding a multiple reference 35 U.S.C. 102 rejection and see MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103.

CLAIM INTERPRETATION: Claim 1 as amended is drawn to an expression vector comprising a polynucleotide encoding for a polypeptide of SEQ ID NO:9 which hydroxylates the 24-position of an oleanane type triterpene. MPEP 2111 directs the examiner to give claims their broadest reasonable interpretation. As noted above, in view of the recitation of the grammatically indefinite article "a" in the phrase "a polypeptide of SEQ ID NO:9", this phrase has been interpreted as meaning any contiguous amino acid sequence of SEQ ID NO:9 of as few as two amino acids. In view of this broad but reasonable interpretation, the phrase "a polynucleotide encoding a polypeptide of SEQ ID NO:9" need only encode at least two contiguous amino acids of SEQ ID NO:9 and can encode any additional amino acid sequence at its 5'- and/or 3'-end(s). The encoded polypeptide is required to have the activity of hydroxylating the 24-position of an oleanane-type triterpene.

The reference of Steele teaches a baculovirus expression vector with a nucleic acid comprising a *CYP93E1* gene (p. 147, column 1, bottom), encoding a cytochrome

P450 enzyme, wherein the *CYP93E1* gene of Steele encodes contiguous amino acids 42-513 of SEQ ID NO:9 (see Appendix A sequence alignment). Since amino acids 42-513 of SEQ ID NO:9 are a substantial portion of the polypeptide, this fragment is considered to be of a sufficient length to hydroxylate the 24-position of an oleanane-type triterpene. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

The reference of Shibuya is cited in accordance with MPEP 2131.01 and MPEP 2124 as showing that the polypeptide encoded by the *CYP93E1* gene of Steele encodes a polypeptide that hydroxylates position 24 of  $\beta$ -amyrin (p. 951, column 2, bottom).

This anticipates claim 1 as written.

RESPONSE TO ARGUMENT: At p. 18 of the instant remarks, applicant argues the reference of Steele fails to teach an expression vector encoding "a polypeptide of SEQ ID NO:9". However, contrary to applicant's position, in view of a broad, but reasonable interpretation of the claim, particularly with respect to the phrase "a polypeptide of SEQ ID NO:9", the reference of Steele anticipates the claimed invention.

**[14]** Claim(s) 3 and 5 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Steele (*supra*) in view of La Rosa et al. (US Patent Application Publication 2004/0031072 A1, February 2004; cited in the 4/11/08 PTO-892) and Schopfer et al. (*FEBS Lett.* 432:182-186, 1998; cited in the 4/11/08 PTO-892; "Schopfer").

Claim 3 is drawn to a transformant in which a host is transformed with the expression vector described in claim 1, wherein the host is a microorganism.

Claim 5 limits the microorganism of claim 3 to being yeast.

The relevant teachings of Steele are set forth above. Steele does not expressly teach a microorganism or yeast as an expression host.

Schopfer teaches recombinant expression of a soybean cytochrome P450-dependent enzyme in a yeast host cell optimized for expression of cytochrome P450 enzymes (p. 182, abstract and p. 183, column 2, bottom).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Steele and Schopfer to transform a yeast host cell with an expression vector comprising the polynucleotide of Steele. One would have been motivated to do this because of the yeast of Schopfer is optimized for cytochrome P450 recombinant protein expression. One would have a reasonable expectation of success to transform yeast with an expression vector comprising the polynucleotide of Steele because of the results of Steele and Schopfer. Therefore, claims 3 and 5, drawn to the transformant as described above would have been obvious to one of ordinary skill in the art.

RESPONSE TO ARGUMENT: Beginning at p. 18 of the instant remarks, applicant argues the combination of references fails to teach an expression vector encoding "a polypeptide of SEQ ID NO:9". However, contrary to applicant's position, in view of a broad, but reasonable interpretation of the claims, the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention.

**[15]** Claim(s) 6, 8, and 10 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Morita et al. (*Eur. J. Biochem.* 267:3453-3460, 2000; cited in the 4/11/08 PTO-892; "Morita") in view of GenBank Accession Number AAA77063 (October, 1995; "GenBank AAA77063") and as evidenced by Invitrogen pYES2 vector map (obtained from the internet web address [tools.invitrogen.com/content/sfs/vectors/pyes2\\_map.pdf](http://tools.invitrogen.com/content/sfs/vectors/pyes2_map.pdf), last viewed on 11/3/08; "pYES2 map").

CLAIM INTERPRETATION: Claim 6 as amended is drawn to a co-expression vector comprising a polynucleotide encoding for "a polypeptide of SEQ ID NO:9" and a beta-amylin synthase gene. As noted above, MPEP 2111 directs the examiner to give claims their broadest reasonable interpretation. In view of the recitation of the grammatically indefinite article "a" in the phrase "a polypeptide of SEQ ID NO:9", this phrase has been interpreted as meaning any contiguous amino acid sequence of SEQ ID NO:9 of as few as two amino acids. In view of this broad but reasonable interpretation, the phrase "a polynucleotide encoding a polypeptide of SEQ ID NO:9" need only encode at least two contiguous amino acids of SEQ ID NO:9 and can encode

any additional amino acid sequence at its 5'- and/or 3'-end(s). The function of the encoded polypeptide is unlimited.

Claim 8 is drawn to a transformant in which a host is transformed with the expression vector described in claim 6, wherein the host is a microorganism.

Claim 10 limits the microorganism of claim 8 to yeast.

The reference of Morita teaches the cloning of PSY gene (a beta-amyrin synthase gene) into vector pYES2 and use of the resulting vector to transform *S. cerevisiae* (p. 3453, abstract and p. 3455, column 1). Evidentiary reference pYES2 map is cited as showing the pYES2 vector comprises a URA3 gene, encoding a URA3 polypeptide, however, the source and sequence of the URA3 gene is not disclosed.

GenBank AAA77063 discloses the sequence of *S. cerevisiae* URA3, which shares at least two contiguous amino acids with SEQ ID NO:9. For example, the first two amino acids of SEQ ID NO:9 are Met-Leu, which are present at positions 149-150 of GenBank AAA77063. In view of a broad, but reasonable interpretation of the claims, the *S. cerevisiae* URA3 gene is encompassed by "a polynucleotide encoding for a polypeptide of SEQ ID NO:9" as recited in claim 6.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Morita and GenBank AAA77063 to practice the method of Morita, wherein the pYES2 expression vector encodes an *S. cerevisiae* URA3 polypeptide. One would have been motivated to do this because Morita uses a *S. cerevisiae* cell for recombinant protein expression and thus the use of the *S. cerevisiae* URA3 polypeptide would ensure compatibility. One would have had a reasonable

expectation of success to practice the method of Morita, wherein the pYES2 expression vector encodes an *S. cerevisiae* URA3 polypeptide because of the results of Morita and GenBank AAA77063. Therefore, claims 6, 8, and 10, drawn to the expression vector and transformant as described above, would have been obvious to one of ordinary skill in the art at the time of the invention.

### ***Conclusion***

**[16]** Status of the claims:

Claims 1-3, 5-8, and 10-16 are pending.

Claims 12-16 are withdrawn from consideration

Claims 1, 3, 5-6, 8, and 10 are rejected.

Claims 2 and 7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 11 would appear to be in a condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-

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272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/  
Primary Examiner, Art Unit 1656





Db 175 ATACCCCTTGCTGGGACACGCGCCATATGTCCTGCTACTGCTCCACGAAGCATTTGACAAG 234

Qy 61 LeuSerLeuArgTyrGlyProLeuIleHisValMetIleGlySerLysHisValValVal 80  
 |||

Db 235 CTATCACTGCGCTATGACCCCTTGATCCACGTCAATGATCGTTCCGAAGCACGTTGGTGTG 294

Qy 81 AlaSerSerAlaGluThrAlaLysGlnIleLeuLysThrSerGluGluAlaPheCysAsn 100  
 |||

Db 295 GCGTCTGCGGGGAGACGCGCAAGCAGATCCTCAAAACCTCGGAGGAGGCATTCTCAAC 354

Qy 101 ArgProLeuMetIleAlaSerGluSerLeuThrTyrGlyAlaAlaAspTyrPhePheIle 120  
 |||

Db 355 CGTCCCTTAATGATAGCGAGCGAGAGCCTAACTACGCGCGGCGGACTACTTCTTCATC 414

Qy 121 ProTyrGlyThrTyrTrpArgPheLeuLysLysLeuCysMetThrGluLeuLeuSerGly 140  
 |||

Db 415 CCTTACGGCACACTGCGCGTTCTGAAGAAGCTGCGATGACCGAGCTTCTGAGCGGG 474

Qy 141 LysThrLeuGluHisPheValArgIleArgGluSerGluValGluAlaPheLeuLysArg 160  
 |||

Db 475 AAGACCTTGGAGCATTTCTGTGAGAAATCCGCGAGAGCGAGTGGAGGCGTCTCTCAGAGA 534

Qy 161 MetMetGluIleSerGlyAsnGlyAsnTyrGluValValMetArgLysGluLeuIleThr 180  
 |||

Db 535 ATGATGGAGATTTCAAGCAATGGAATACGAGGTGGTGATGAGGAAGAGAGCTCATACG 594

Qy 181 HisThrAsnAsnIleIleThrArgMetIleMetGlyLysLysSerAsnAlaGluAsnAsp 200  
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Db 595 CACACGAATAACATCATCACGAGGATGATAATGGGGAAGAGAGTAATCGCGAAACGAT 654

Qy 201 GluValAlaArgLeuArgLysValValArgGluValGlyGluLeuLeuGlyAlaPheAsn 220  
 |||

Db 655 GAGGTGGCCAGGTTGAGGAGGTGTTGAGGAGGTGCGGGAGTTGCTTGGGCGCTTAAAC 714

Qy 221 LeuGlyAspValIleGlyPheMetArgProLeuAspLeuGlnGlyPheGlyLysLysAsn 240  
 |||

Db 715 TTGGGGATGTTATTTGGGTTTATGAGGCTTTGGATCTGCAAGGGTTTGGGAAGAGAAC 774

Qy 241 MetGluThrHisHisLysValAspAlaMetMetGluLysValLeuArgGluHisGluGlu 260  
 |||

Db 775 ATGGAACTCACCAAGGTGGATGCGATGATGGAAGGTGTTGAGGAGCATGAGGAG 834

Qy 261 AlaArgAlaLysGluAspAlaAspSerAspArgLysLysAspLeuPheAspIleLeuLeu 280  
 |||

Db 835 GCTAGGGCTAAGGAAGATGCTGACTCTGATAGGAAGAAGGATCTTTTGATATTTTGTG 894

Qy 281 AsnLeuIleGluAlaAspGlyAlaAspAsnLysLeuThrArgGluSerAlaLysAlaPhe 300  
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Db 895 AACCTCATTTGAAGCTGATGGTGCTGACAAATAGCTCACTAGAGAGAGTGCACAGCCTTT 954

Qy 301 AlaLeuAspMetPheIleAlaGlyThrAsnGlyProAlaSerValLeuGluTrpSerLeu 320  
 |||

Db 955 GCTCTGGACATGTTATCGCGGGCAACACGGCCCGCAAGCGTCTAGAGTGGTCACTG 1014

Qy 321 AlaGluLeuValArgAsnProHisValPheLysLysAlaArgGluGluIleGluSerVal 340  
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Db 1015 CCGGAGCTGGTGAGAAAACCCACGTTTCAAGAAGCAAGGAAGAGATTGAGTCAGTG 1074

Qy 341 ValGlyLysGluArgLeuValLysGluSerAspIleProAsnLeuProTyrLeuGlnAla 360  
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Db 1075 GTAGGCAAGGAAGAGCTGGTCAAGGAATCAGACATTCCCAACCTACCTACCTCAGACA 1134

Qy 361 LeuLeuLysGluThrLeuArgLeuHisProProThrProIlePheAlaArgGluAlaMet 380  
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Db 1135 GTGCTGAAGGAACCTTAAAGCTGACACCGGCAACCCCAATATTCGCAAGAGAGCATG 1194

Qy 381 ArgThrCysGlnValGluGlyTyrAspIleProGluAsnSerThrIleLeuIleSerThr 400  
 |||

Db 1195 CGAACATGCCAGGTTGAAGGCTACGACATTCGCGAAATTCACATATTTGATCAGCACA 1254

Qy 401 TrpAlaIleGlyArgAspProAsnTyrTrpAspAspAlaLeuGluTyrLysProGluArg 420  
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Db 1255 TGGGCCATTGGTAGGGATCCAAATTACTGGGATGACGCACTCGAGTACAAGCCGGAGAGG 1314  
 Qy 421 PheLeuPheSerAspAspProGlyLysSerLysIleAspValArgGlyGlnTyrTyrGln 440  
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||  
 Db 1315 TTCTTGTTCTCCGACGACCCGGGCAAGAGCAAGATTGACGTGAGGGGGCAGTACTATCAG 1374  
 Qy 441 LeuLeuProPheGlySerGlyArgArgSerCysProGlyAlaSerLeuAlaLeuLeuVal 460  
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||  
 Db 1375 CTCTTGCCCTTTGGGAGCGGGAGAAGAAGCTGCCCGGAGCCTCGCTAGCGTTGCTTGTTC 1434  
 Qy 461 MetGlnAlaThrLeuAlaSerLeuIleGlnCysPheAspTrpIleValAsnAspGlyLys 480  
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 Db 1435 ATGCAAGCAACGCTAGCGAGTTTGATCCAGTGCTTCGACTGGATCGTTAATGATGGTAAA 1494  
 Qy 481 AsnHisHisValAspMetSerGluGluGlyArgValThrValPheLeuAlaLysProLeu 500  
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 Db 1495 AACCATCATGTTGACATGTCTGAGGAAGGGAGGGTGACTGTGTTTTTGGCCAAAGCCACTC 1554  
 Qy 501 LysCysLysProValProArgPheThrProPheAlaAla 513  
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||  
 Db 1555 AAGTGCAGACCTGTTCCGCGTTTCACTCCGTTTCGCTGCC 1593